Avancées et défis de l'automatisation du protocole

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Johnson&Johnson
Innovative Medicine

CDISC GUF Paris 25 juin 2024

Agenda

- Introduction/Notion de protocole électronique
- Avancées/Etat des connaissances
- Défis/limitations
- Présentation d’un outil: Open Study Builder
- Conclusion
- Questions

Introduction

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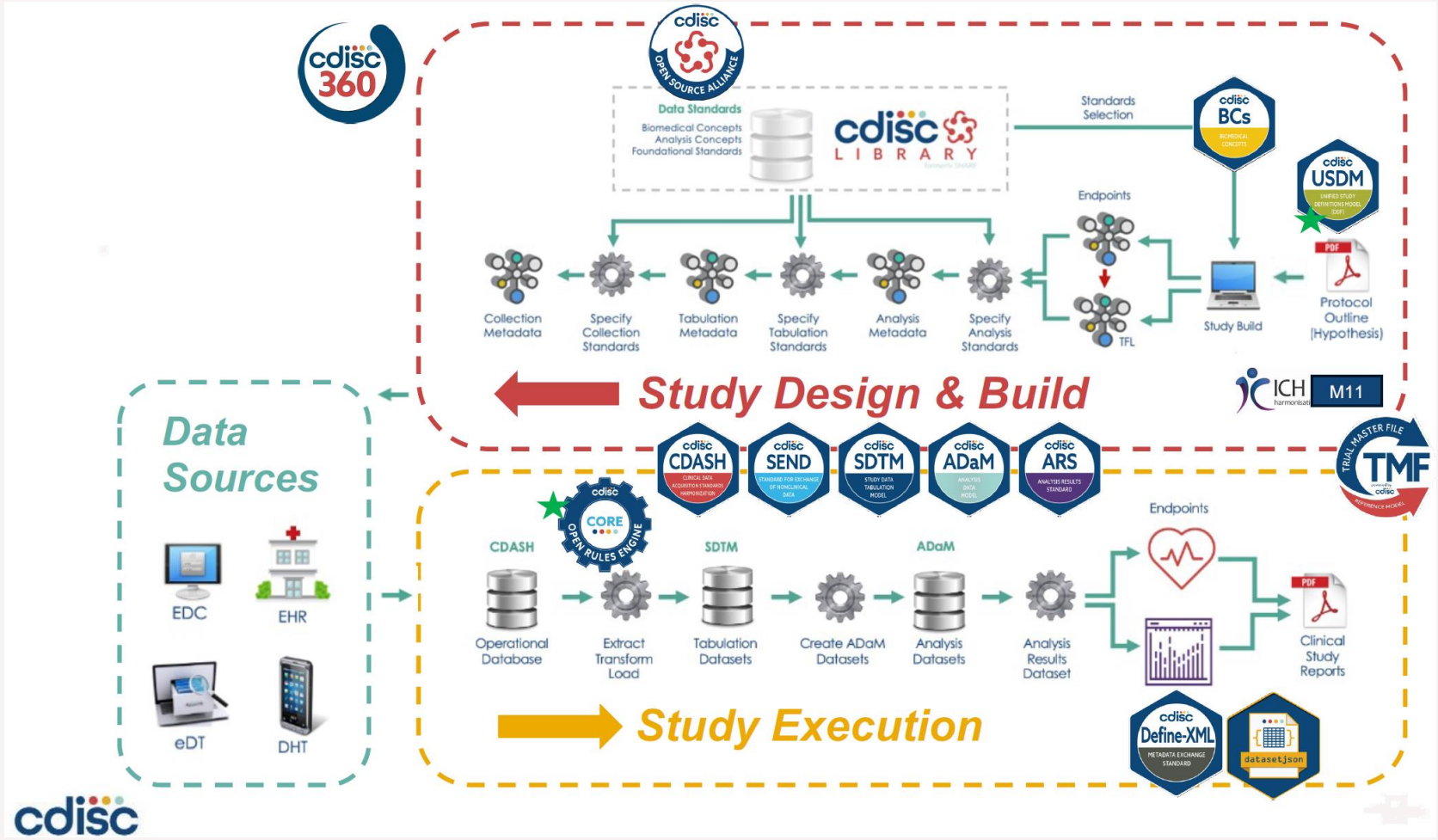
Vue d'ensemble des ressources CDISC



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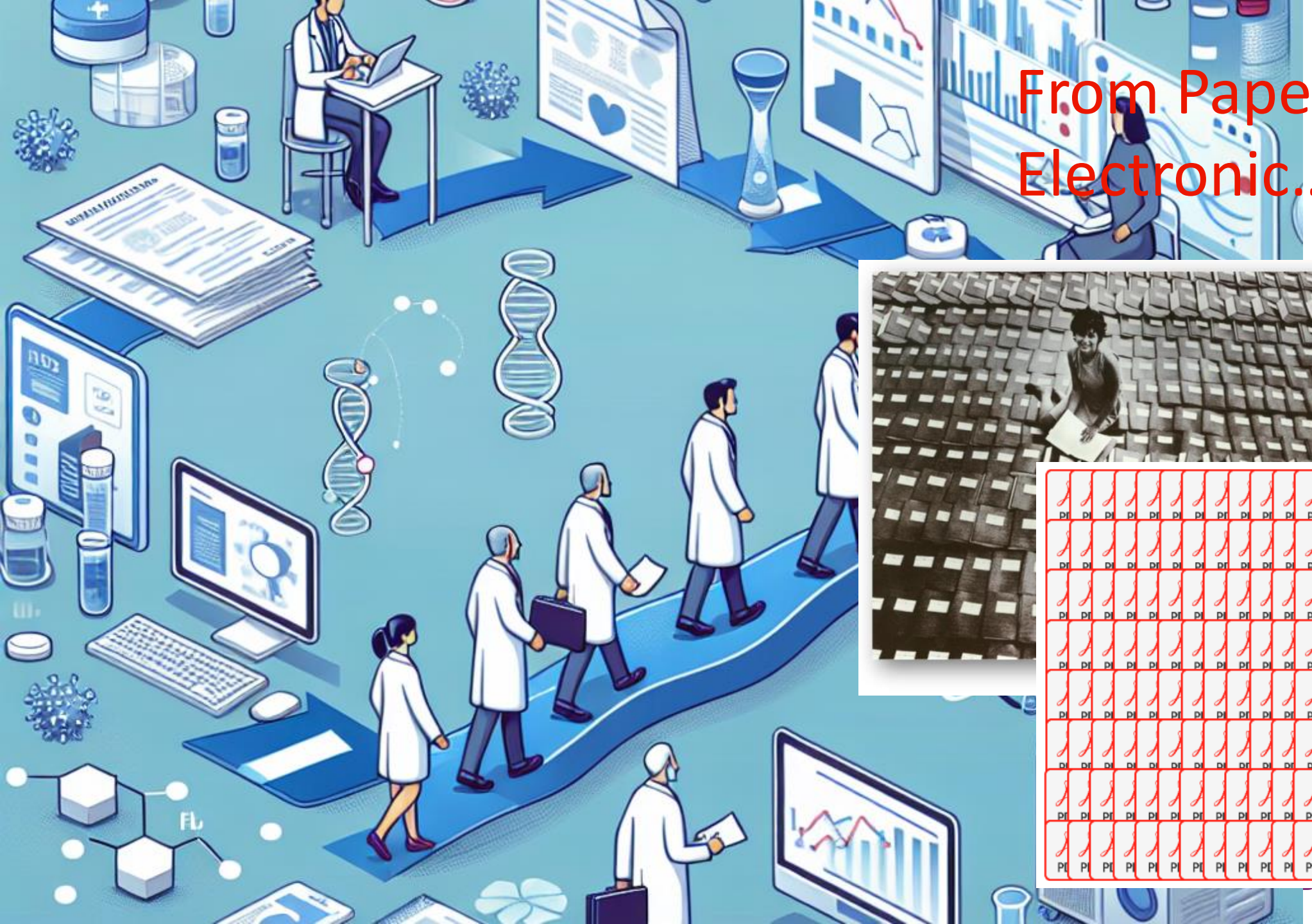
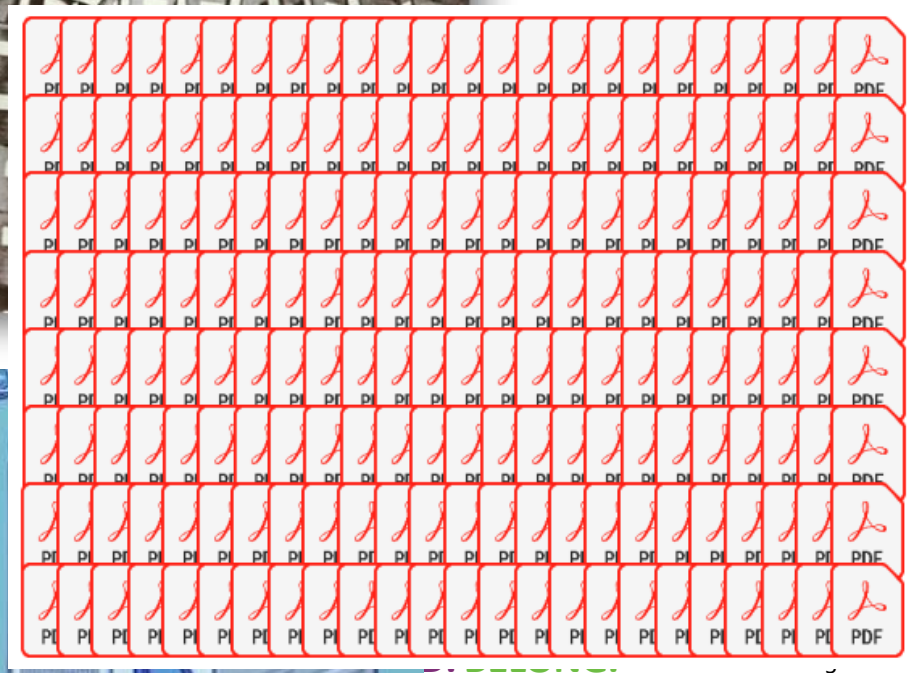
From Paper to Electronic…





Avancées/
Etat des connaissances

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Collaboration/Partenaires

Vulcan FHIR® Accelerator mets en relation CDISC, HL7, and ICH M11 dans un projet de numérisation d'échange des protocoles de recherche clinique

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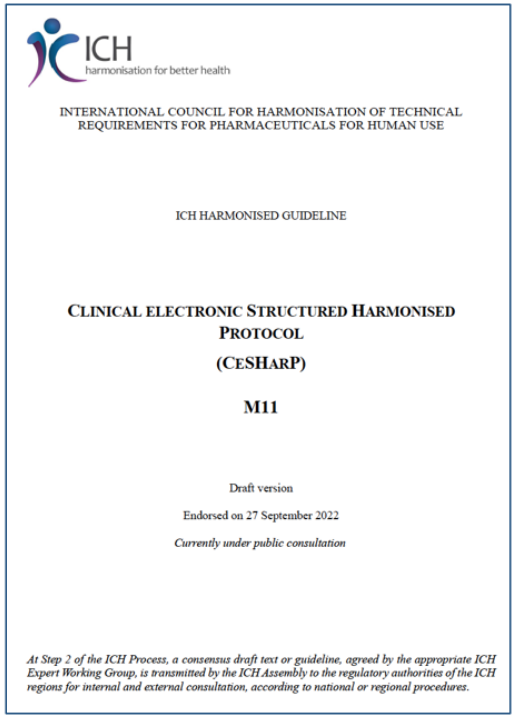
ICH - Clinical electronic Structured Harmonized Protocol (CeSHarP)



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL

(CESHARP)

M11

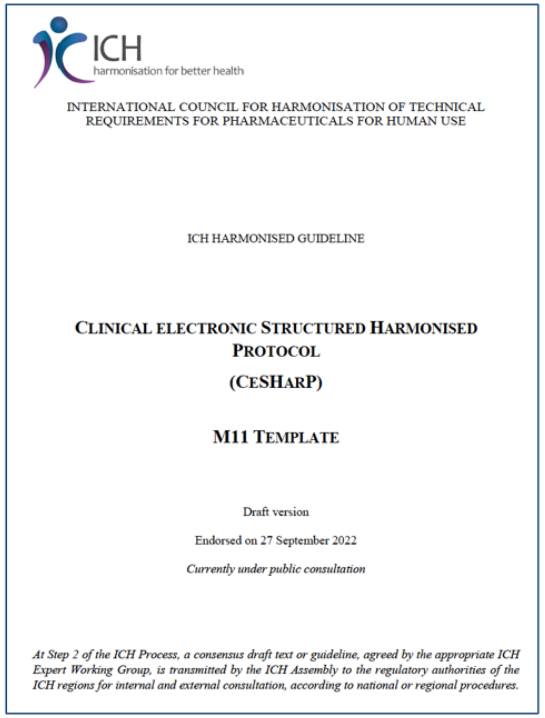
Draft version

Endorsed on 27 September 2022

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

Provides background, purpose, and scope as a guideline



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(CESHARP)

M11 TEMPLATE

Draft version

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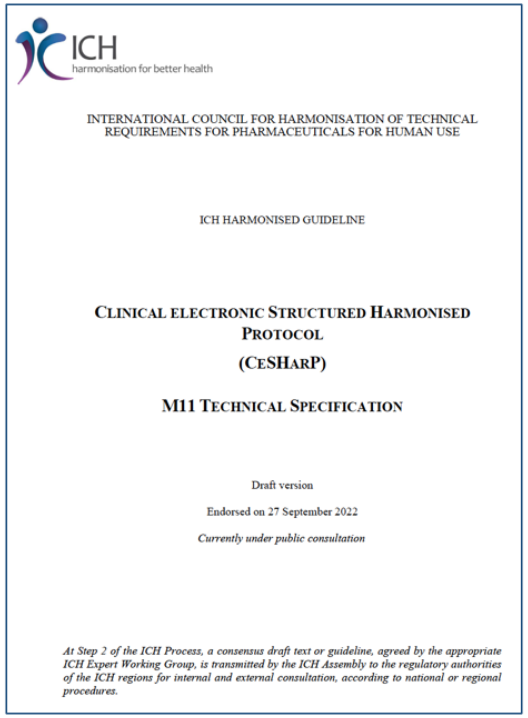
Provides the written format for the Interventional Clinical Trial Protocol Template



ICH
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CLINICAL ELECTRONIC STRUCTURED HARMONISED PROTOCOL

(CESHARP)

M11 TECHNICAL SPECIFICATION

Draft version

Endorsed on 27 September 2022

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Provides the technical representation aligned with the guideline and protocol template

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M11 Exemple

Template Specification

Protocol Full Title:	[Protocol Full Title] The protocol should have a descriptive title that identifies the scientific aspects of the trial sufficiently to ensure it is immediately evident what the trial is investigating and on whom, and to allow retrieval from literature or internet searches.
Sponsor Confidentiality Statement:	[Sponsor Confidentiality Statement] Insert the Sponsor's confidentiality statement, if applicable, otherwise delete.
Protocol Number:	[Protocol Number] A unique alphanumeric identifier for the trial, designated by the Sponsor, is a standard part of trial data, and should be included for most trials.
Version:	[Version] An optional field for use by the Sponsor at their discretion.
Amendment Number:	[Amendment Number] Enter the amendment number. If this is the original instance of
Trial Phase:	[Trial Phase] [Description of Trial Phase Other] Acceptable entries are: "Early Phase 1", "Phase 1", "Phase 1/Phase 2", "Phase 2", "Phase 2/Phase 3", "Phase 3", "Phase 4",
Compound Number(s):	[Compound Number] Enter the Sponsor's unique identifier for investigational compound(s) in the trial. Add or delete additional fields as needed.
Compound Name(s):	[Nonproprietary Name]. [Proprietary Name]. [Additional Proprietary Name] Delete this line from the table if a nonproprietary name has not yet been assigned. Omit proprietary name fields if not yet established.
Trial Phase:	[Trial Phase] [Description of Trial Phase Other] Acceptable entries are: "Early Phase 1", "Phase 1", "Phase 1/Phase 2", "Phase 2", "Phase 2/Phase 3", "Phase 3", "Phase 4",

Technical Specification

Term (Variable)	Trial Phase
Data Type	Pick list
Topic, Value or Header	D
Definition	
User Guidance	For trials combining investigational drugs or vaccines with devices, classify according to the phase of drug development.
Conformance	Required
Cardinality	
Relationship content from ToC representing the protocol hierarchy	Title Page
Relationship (reference to high level conceptual model)	
Value	Early Phase 1 Phase 1 Phase 1/Phase 2 Phase 2 Phase 2/Phase 3 Phase 3 Phase 4 Other
Business rules	**Value Allowed:** yes **Relationship:** n/a **Concept:** Protocol short title
Duplicate field in other sections	

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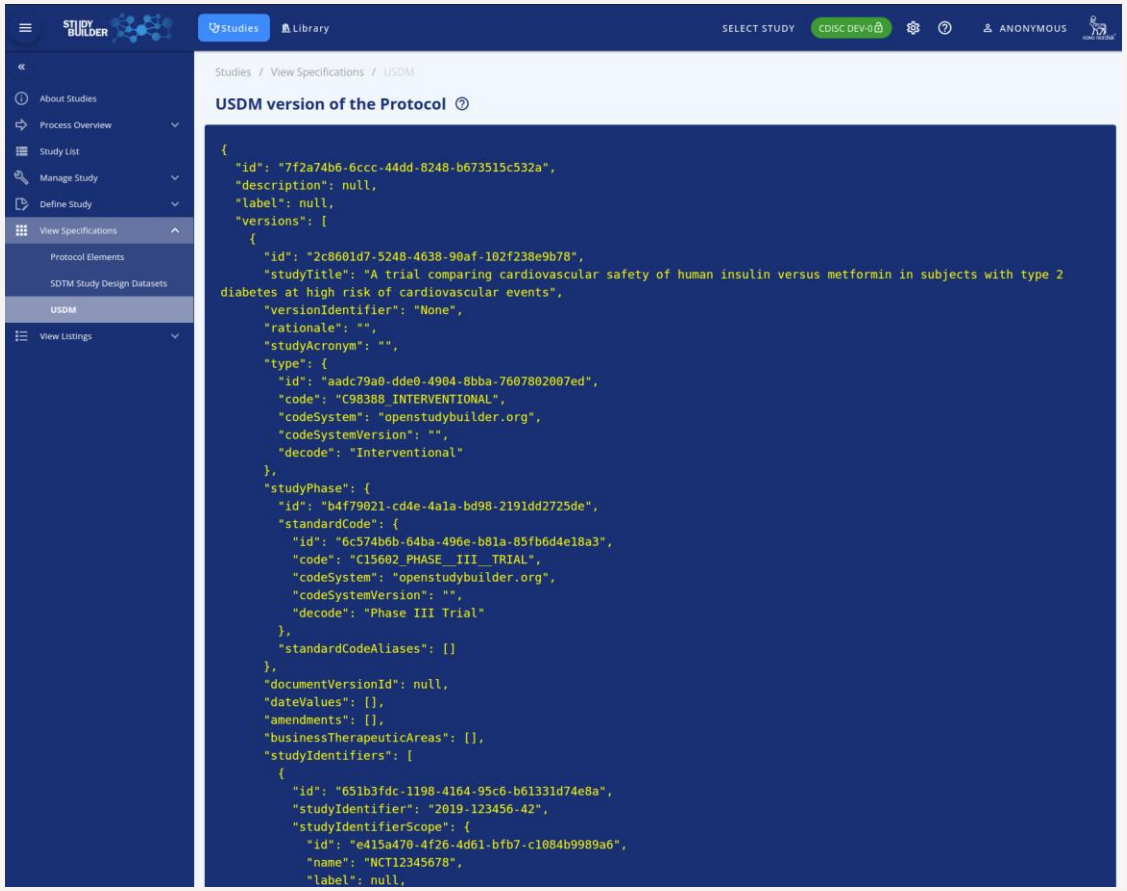
Digital Study Design et USDM

Unified Study Definitions Model (USDM)

- Holds many aspects of the study design
- Facilitates interoperability between systems
- Schedule of Activities = digital backbone of the protocol
- Link Schedule of Activities to standard Concepts
- Support study design activities



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Digital Data Flow (DDF)

Digital Data Flow Initiative will help modernize clinical trials by enabling a digital workflow with protocol digitization. This initiative establishes a foundation for a future state of automated & dynamic readiness that can transform the drug development process.

TransCelerate BIOPHARMA INC.

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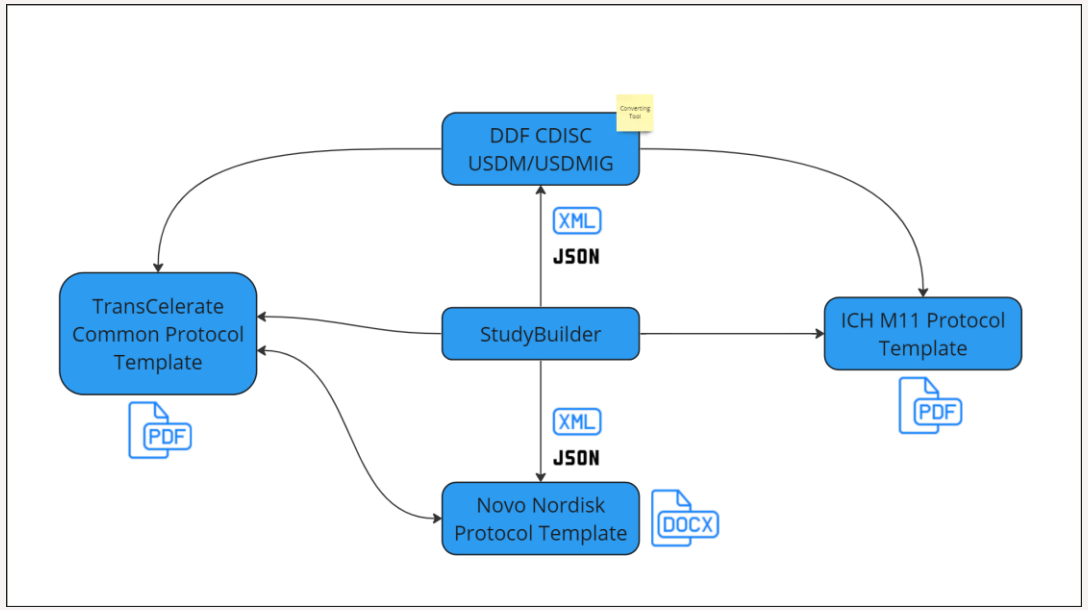
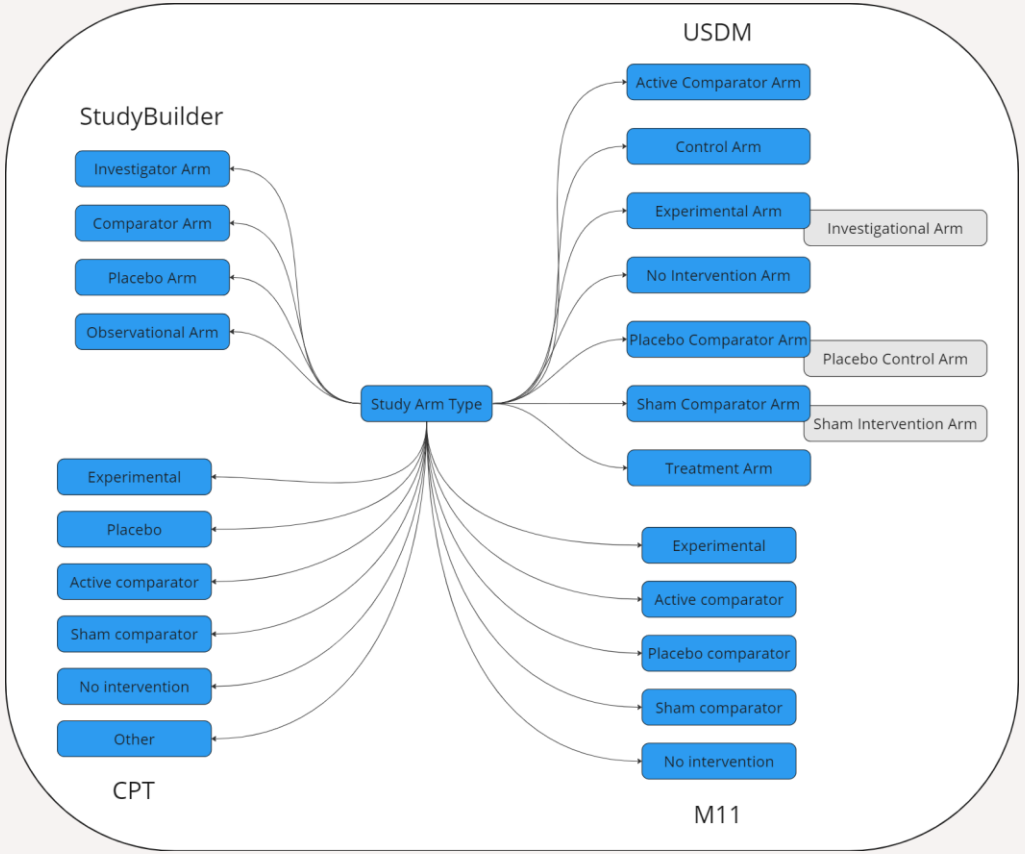
Digital Data Flow (DDF)

Biomédical Concepts (BCs)

Clé de voute d'un système «End to End »





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Défis

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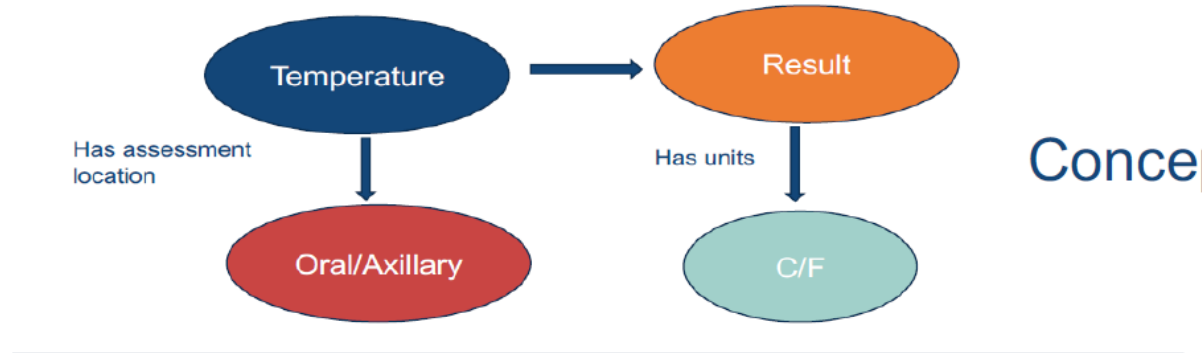
Connecter le design aux résultats

We need well defined Concepts:

- Standardize the meaning and semantics of data
- Regardless of data representation

Concepts will:

- Link to the **Schedule of Activities**
- Provide consistent implementation
- Facilitate automation
- Prevent AI from hallucinating



VSTEST	VSTESTCD	VSORRES	VSUNIT	VSLOC
Temperature	TEMP	101.3	F	ORAL

Representation

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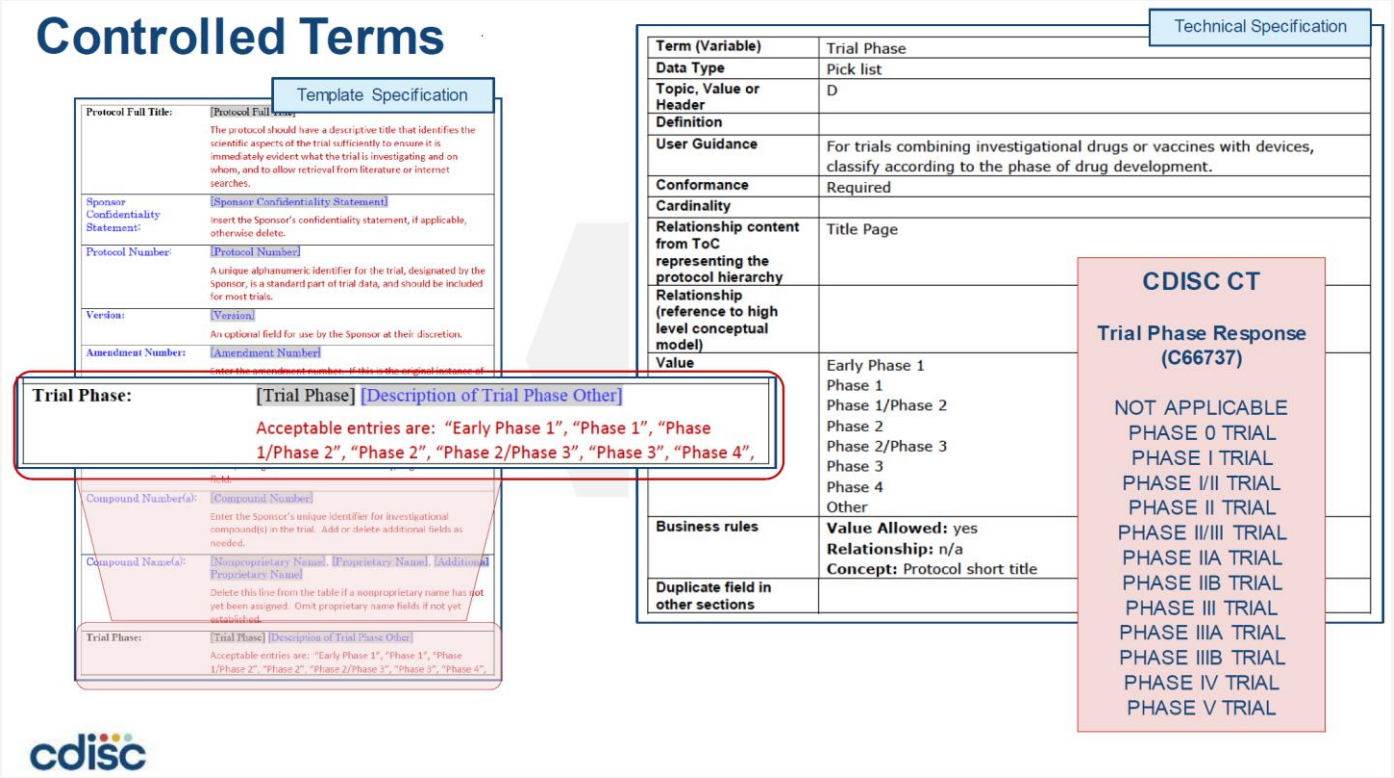
Harmonisation des Controlled Terminology

Mapping data from various formats often breaks down:

- The meaning and terminology do not match (e.g. eHR to SDTM)
- Mapping between common data models is only a part of the solution



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Les Formats M11 et Transcelerate: à différente vitesse

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Gestion des différentes versions de métadonnées de protocole

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Adhésion de l’utilisateur

Historiquement les Medical Writter travaillent sur Word.

Résistances au changement, à l’utilisation d’outil plus complexe.

Différentes approches:

- Chalenge en interne: dev de nouveau outils
- VS connexion avec un outil existant (mais vieillissant)

Outils

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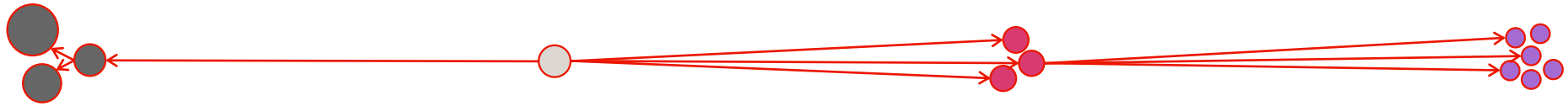
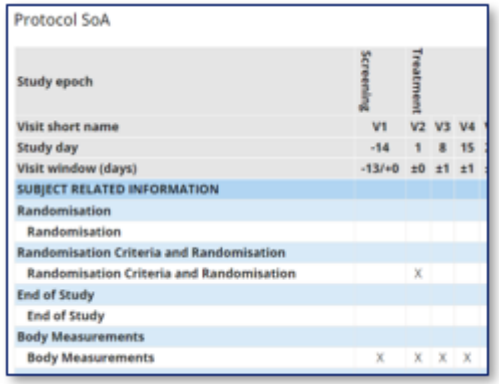
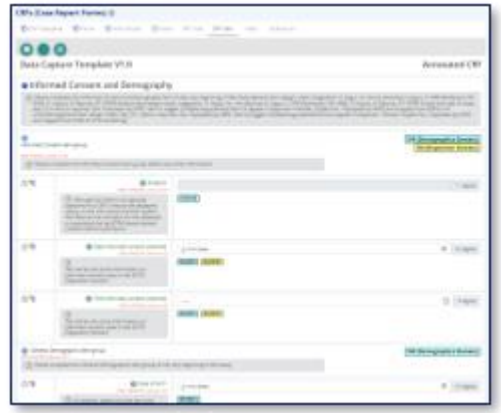
What is the key elements of OpenStudyBuilder supporting protocol automation

- **Library module**
  - CDISC and sponsor terminology including sponsor preferred synonyms
  - Biomedical Concepts named as Activity Concepts
  - Syntax templates, to manage human readable structured protocol text
- **Study module**
  - General Study attributes in scope for the protocol
  - Study Design and SoA
  - Objectives and Endpoints
  - In- and Exclusion criteria

Schedule of Activities (SoA) at multiple levels







Protocol SoA

- For the high level SoA in protocol section 1.2
- Main purpose is for the investigator and site staff to get an overview of the operational schedule

Detailed SoA

- Specifying the semantic data observations to be collected in the study – but not specific to representation in ADaM, SDTM or data collection
- Will be part of protocol section 8 and appendixes or other supplementary documents

Operational SoA

- The data specification to support data collection specification
- Correspond to our existing legacy BCs (Topic Codes)
- Will also related to specific ADaM PARAM/PARAMCD

Data Capture / Collection Specification

- How data is to be collected in the study and when
- What is pre-set, what is collected and how

About Studies
Process Overview
Manage Studies
Define Study
Study Title
Registry Identifiers
Study Properties
Study Structure
Study Population
Study Criteria
Study Interventions
Study Purpose
Study Activities
View Specifications
View Listings

Study Activities (CDISC DEV-0)

Study Activities | Study Activity Instances | Detailed SoA | SoA footnotes | Protocol SoA | Activity Instructions

The detailed SoA describe scheduling of the specific Activities and their grouping for the study

roups

		Screening	Treatment									Follow-up
		V1 ☐	V2 ☐	V3 ☐	V4 ☐	V5 ☐	V6 ☐	V7 ☐	V8 ☐	V9 ☐	V10 ☐	V11 ☐
		-14	1	8	15	22	29	36	43	57	183	213
	Activities	Window	-13/+0	±0	-1/+1	-1/+1	-1/+1	-1/+1	-1/+1	-1/+1	-1/+1	-1/+1	0/+35
>	SUBJECT RELATED INFORMATION												
v	EFFICACY												
v	Laboratory Assessments												
v	Glucose Metabolism												
	HbA1c		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	○
v	Self Measured Plasma Glucose												
v	Self Measured Plasma Glucose												
	Mean Plasma Glucose		○	○	○	○	○	○	○	○	○	○	○
>	SAFETY												

Each level in the Activity hierarchy can be selected for display in the “Protocol SoA”

Studies / Define Study / Study Activities / Protocol SoA

About Studies
Process Overview
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Study Title
Registry Identifiers
Study Properties
Study Structure
Study Population
Study Criteria
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Study Activities
View Specifications
View Listings

Study Activities (CDISC DEV-0)

Study Activities | Study Activity Instances | Detailed SoA | SoA footnotes | Protocol SoA | Activity Instructions

Produce a copy of the SoA compatible with Word

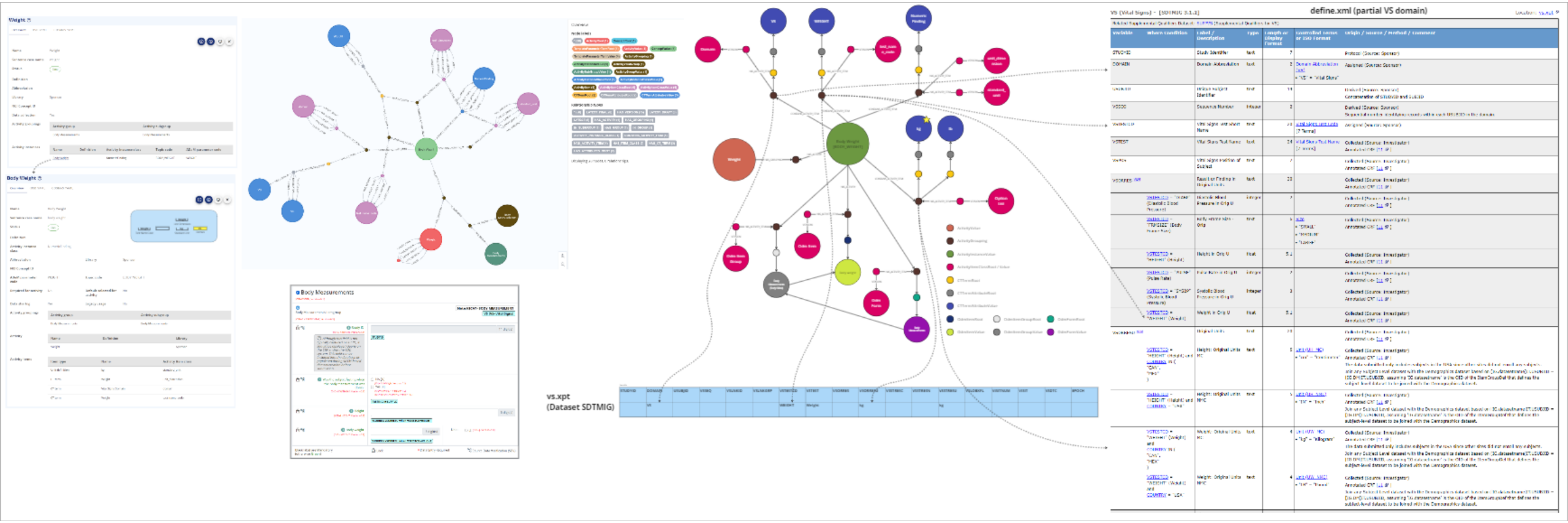
The “Protocol SoA” only displaying the selected activity level of detail as a preview

Protocol SoA

DOWNLOAD DOCX

Procedure	Screening	Treatment									Follow-up
Visit short name	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Study day	-14	1	8	15	22	29	36	43	57	183	213
Visit window (days)	-13/+0	±0	±1	±1	±1	±1	±1	±1	±1	±1	+0/+35
Randomisation											
Randomisation		X									
End of Study											
End of Study											X
Body Measurements											
Body Measurements	X	X	X	X	X	X	X	X	X	X	X
Eligibility Criteria											
Eligibility Criteria	X										
Laboratory Assessments											
Glucose Metabolism	X	X	X	X	X	X	X	X	X	X	
Lipids	X	X			X			X		X	
Biochemistry	X	X			X			X		X	
AE Requiring Additional Data											
Laboratory Assessment	X	X			X			X		X	
Adverse Event											
Adverse Event	X	X	X	X	X	X	X	X	X	X	X
Vital Signs											
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Medical History/Concomitant Illness											

From Activity to CRF and Define…



From Activities…

Weight

Overview | OSB YAML | COSMoS YAML

Name	Weight
Sentence case name	weight
Status	Final
Definition	
Abbreviation	
Library	Sponsor
NCI Concept ID	
Data collection	Yes

Activity groupings

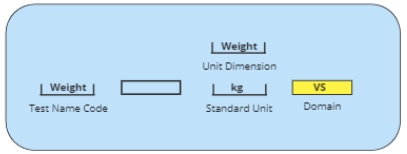
Activity group	Activity subgroup
Body Measurements	Body Measurements

Activity instances

Name	Definition	Activity instance class	Topic code	ADaM parameter code
Body Weight		NumericFinding	BODY_WEIGHT	WEIGHT

Body Weight

Overview | OSB YAML | COSMoS YAML



Name	Body Weight		
Sentence case name	body weight		
Status	Final		
Definition			
Activity instance class	NumericFinding		
Abbreviation		Library	Sponsor
NCI Concept ID			
ADaM parameter code	WEIGHT	Topic code	BODY_WEIGHT
Required for activity	No	Default selected for activity	No
Data sharing	Yes	Legacy usage	No

Activity groupings

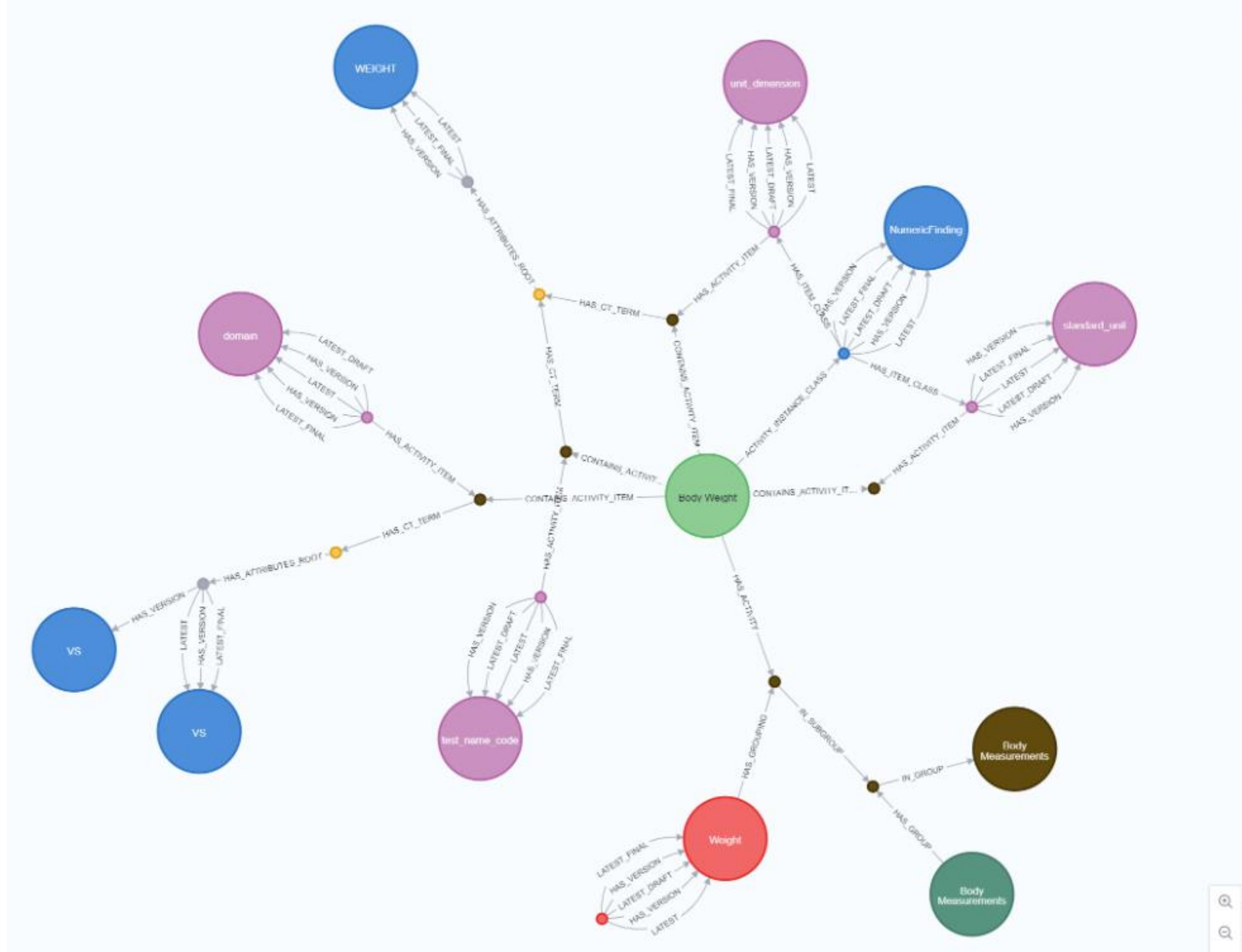
Activity group	Activity subgroup
Body Measurements	Body Measurements

Activity

Name	Definition	Library
Weight		Sponsor

Activity items

Item type	Name	Activity item class
Unit definition	kg	standard_unit
CT term	Weight	unit_dimension
CT term	Vital Signs Domain	domain
CT term	Weight	test_name_code



Overview

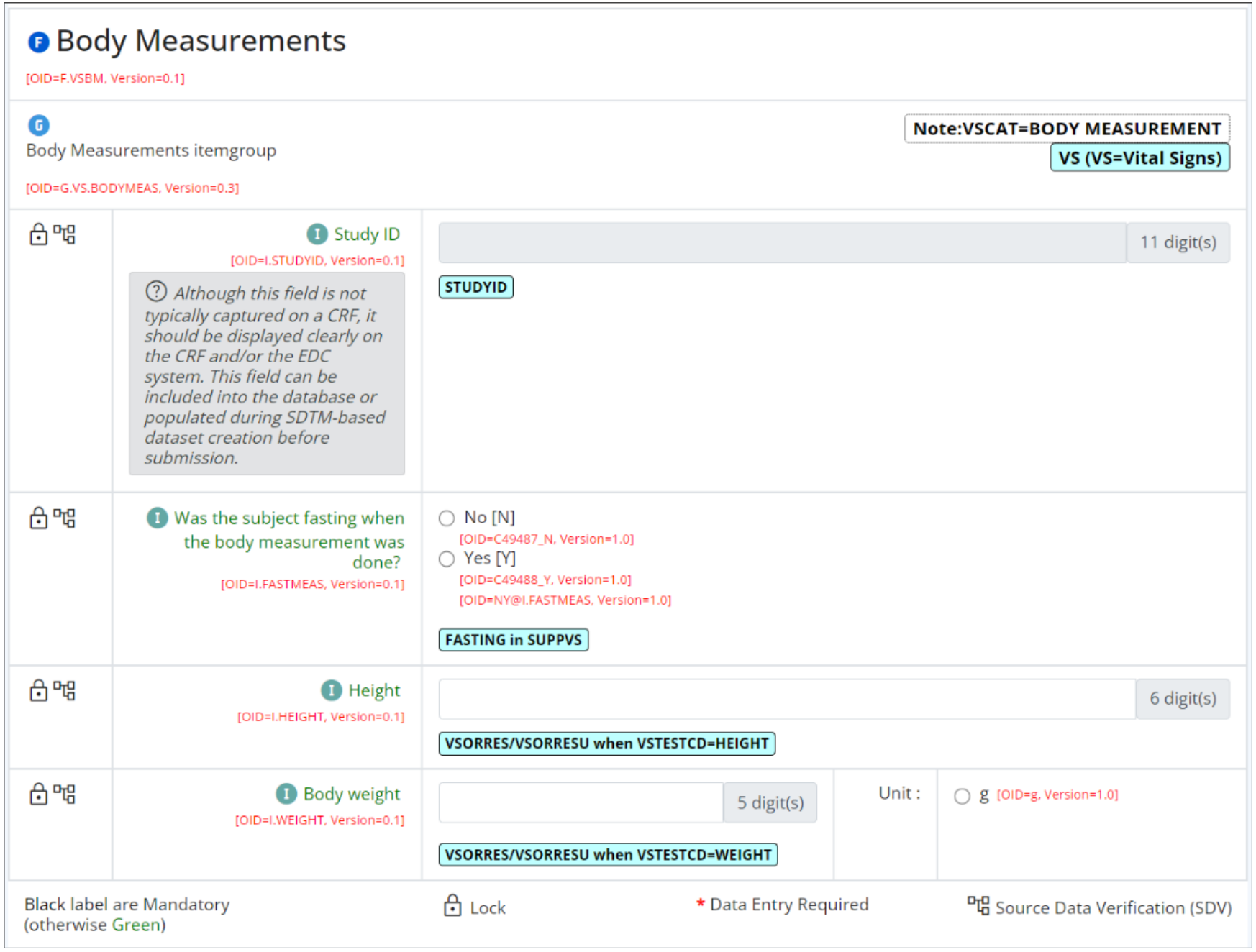
Node labels

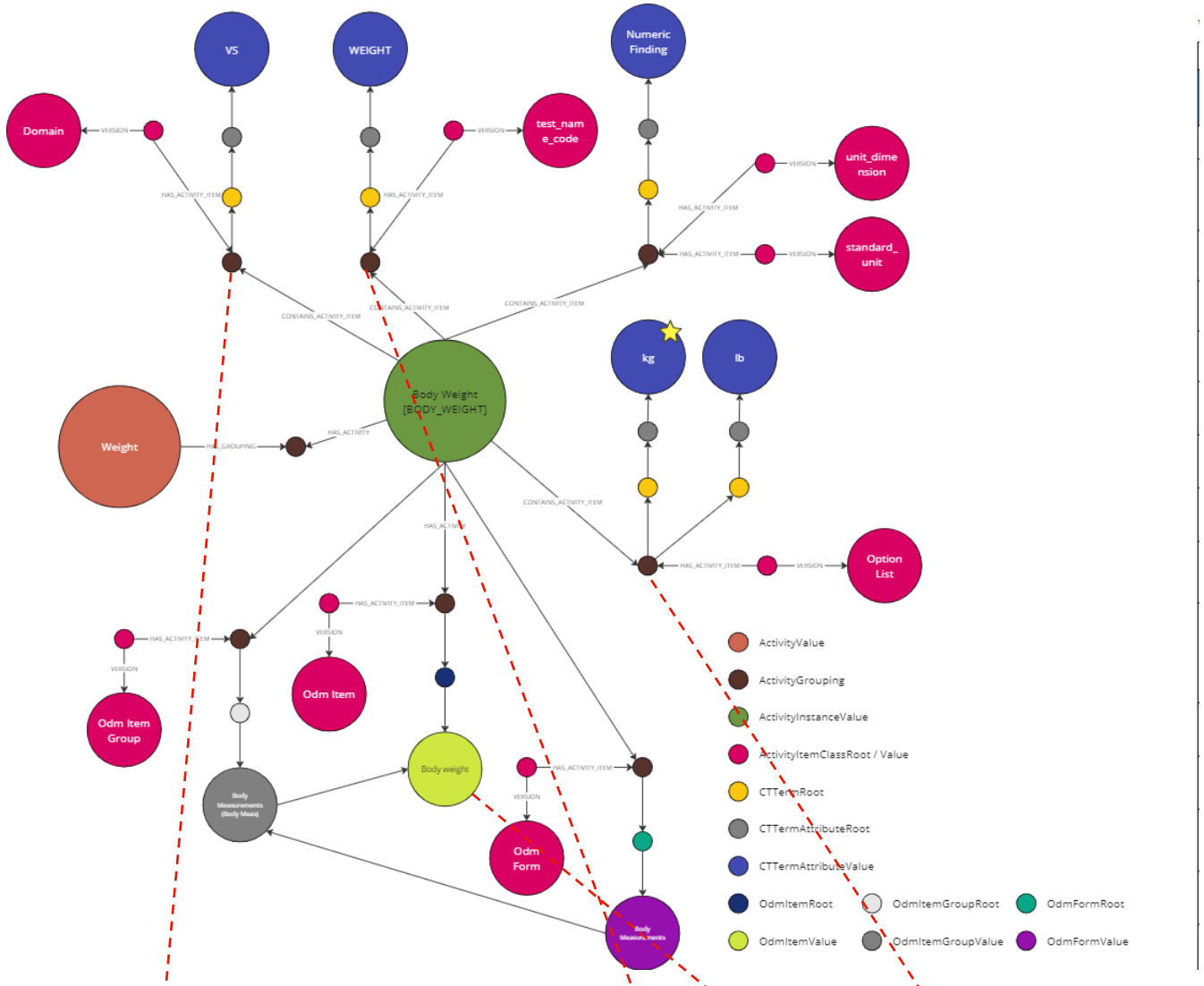
* (28) | ActivityRoot (1) | ConceptRoot (1) | TemplateParameterTermRoot (1) | ActivityValue (1) | ConceptValue (4) | TemplateParameterTermValue (4) | ActivityGrouping (1) | ActivityInstanceValue (1) | ActivityValidGroup (1) | ActivitySubGroupValue (1) | ActivityGroupValue (1) | ActivityInstanceClassRoot (1) | ActivityInstanceClassValue (1) | ActivityItem (4) | ActivityItemClassRoot (4) | ActivityItemClassValue (4) | CTTermRoot (2) | CTTermAttributesRoot (2) | CTTermAttributesValue (3)

Relationship types

* (58) | LATEST_FINAL (8) | HAS_VERSION (15) | LATEST_DRAFT (6) | LATEST (8) | HAS_ACTIVITY (1) | HAS_GROUPING (1) | IN_SUBGROUP (1) | HAS_GROUP (1) | IN_GROUP (1) | ACTIVITY_INSTANCE_CLASS (1) | CONTAINS_ACTIVITY_ITEM (4) | HAS_ACTIVITY_ITEM (4) | HAS_ITEM_CLASS (2) | HAS_CT_TERM (3) | HAS_ATTRIBUTES_ROOT (2)

Displaying 28 nodes, 0 relationships.


Body Measurements
[OID=F.VSBM, Version=0.1]
Body Measurements itemgroup
[OID=G.VS.BODYMEAS, Version=0.3]
Note:VSCAT=BODY MEASUREMENT
VS (VS=Vital Signs)
Study ID
[OID=I.STUDYID, Version=0.1]
Although this field is not typically captured on a CRF, it should be displayed clearly on the CRF and/or the EDC system. This field can be included into the database or populated during SDTM-based dataset creation before submission.
11 digit(s)
STUDYID
Was the subject fasting when the body measurement was done?
[OID=I.FASTMEAS, Version=0.1]
No [N]
[OID=C49487_N, Version=1.0]
Yes [Y]
[OID=C49488_Y, Version=1.0]
[OID=NY@I.FASTMEAS, Version=1.0]
FASTING in SUPPVS
Height
[OID=I.HEIGHT, Version=0.1]
6 digit(s)
VSORRES/VSORRESU when VSTESTCD=HEIGHT
Body weight
[OID=I.WEIGHT, Version=0.1]
5 digit(s)
Unit :
g [OID=g, Version=1.0]
VSORRES/VSORRESU when VSTESTCD=WEIGHT
Black label are Mandatory (otherwise Green)
Lock
* Data Entry Required
Source Data Verification (SDV)



define.xml (partial VS domain)

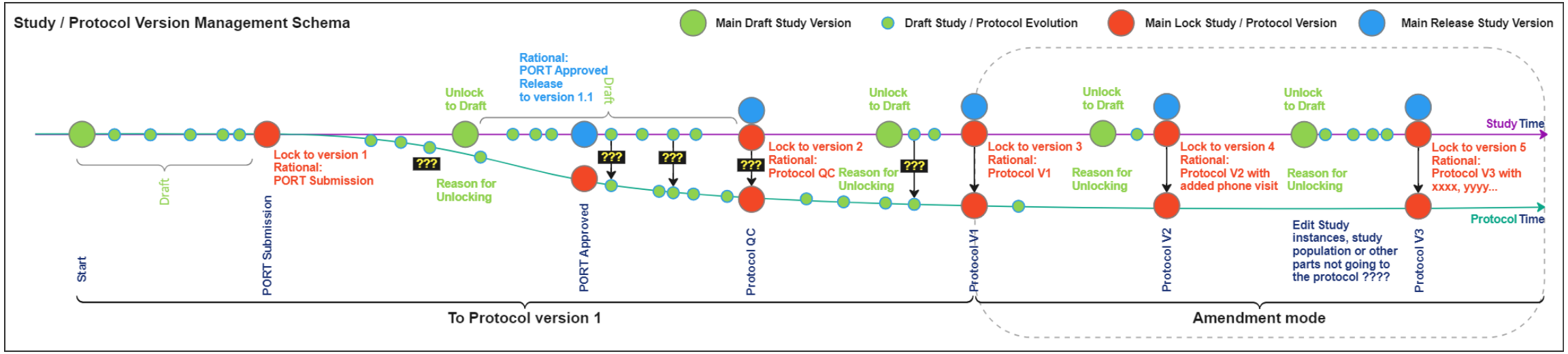
VS (Vital Signs) - [SDTMIG 3.1.2] Location: vs.xpt

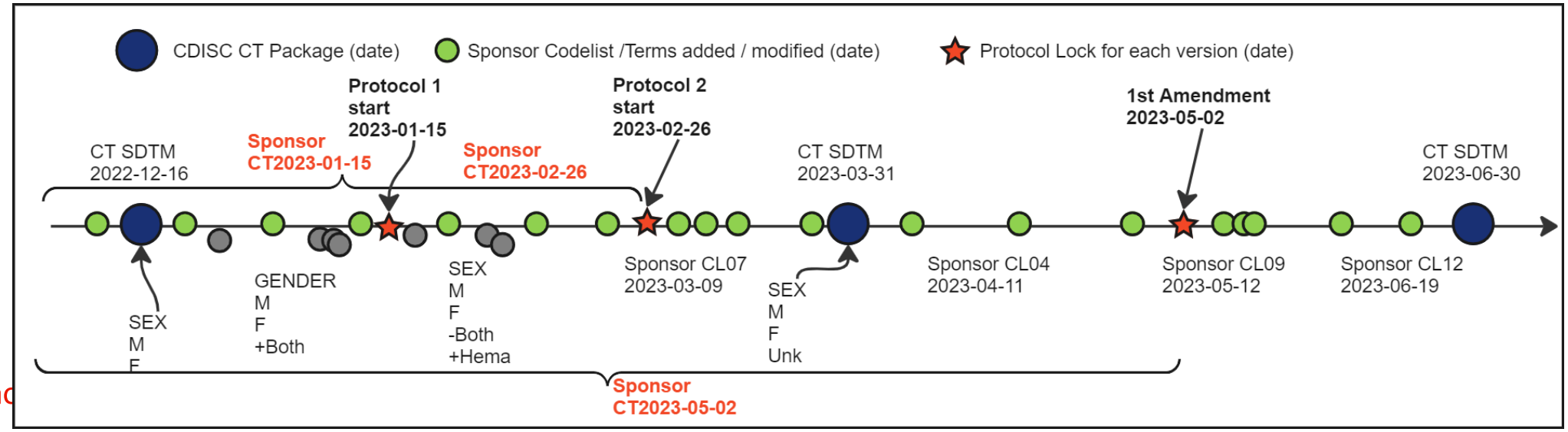
Related Supplemental Qualifiers Dataset: SUPPVS (Supplemental Qualifiers for VS)

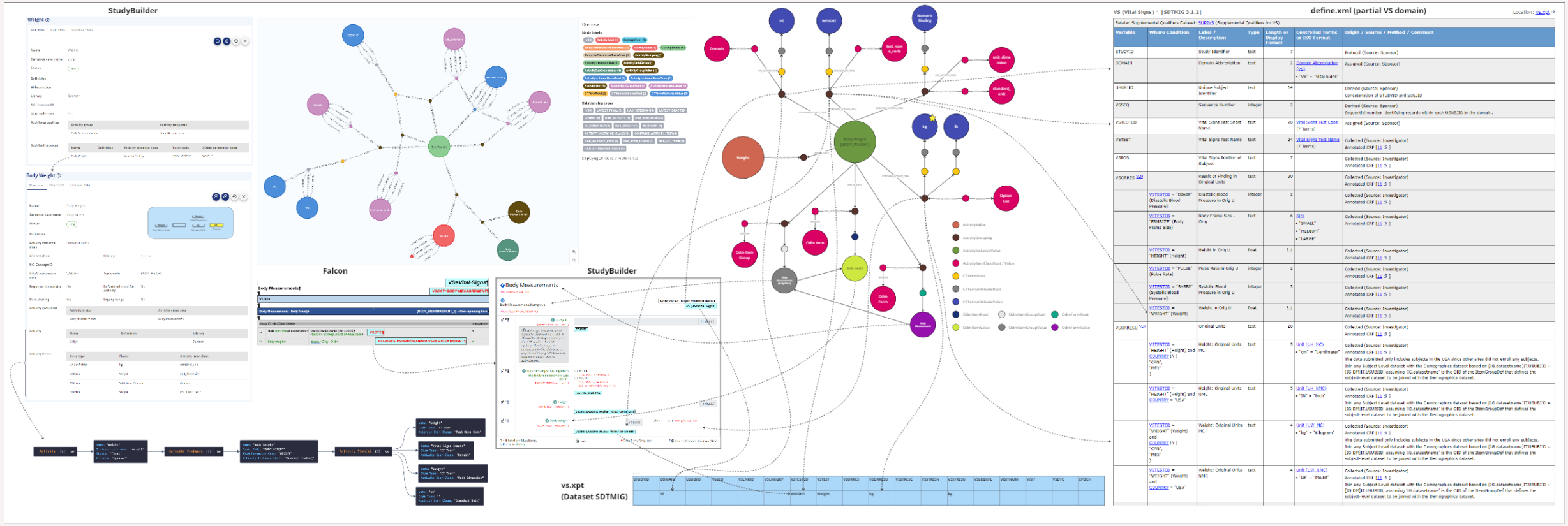
Variable	Where Condition	Label / Description	Type	Length or Display Format	Controlled Terms or ISO Format	Origin / Source / Method / Comment
STUDYID		Study Identifier	text	7		Protocol (Source: Sponsor)
DOMAIN		Domain Abbreviation	text	2	Domain Abbreviation (VS) • "VS" = "Vital Signs"	Assigned (Source: Sponsor)
USUBJID		Unique Subject Identifier	text	14		Derived (Source: Sponsor) Concatenation of STUDYID and SUBJID
VSSEQ		Sequence Number	integer	2		Derived (Source: Sponsor) Sequential number identifying records within each USUBJID in the domain.
VSTESTCD		Vital Signs Test Short Name	text	20	Vital Signs Test Code [7 Terms]	Assigned (Source: Sponsor)
VSTEST		Vital Signs Test Name	text	24	Vital Signs Test Name [7 Terms]	Collected (Source: Investigator) Annotated CRF [11]
VSPOS		Vital Signs Position of Subject	text	7		Collected (Source: Investigator) Annotated CRF [11]
VSORRES VLM		Result or Finding in Original Units	text	30		Collected (Source: Investigator) Annotated CRF [11]
	VSTESTCD = "DIABP" (Diastolic Blood Pressure)	Diastolic Blood Pressure in Orig U	integer	2		Collected (Source: Investigator) Annotated CRF [11]
	VSTESTCD = "FRMSIZE" (Body Frame Size)	Body Frame Size - Orig	text	6	Size • "SMALL" • "MEDIUM" • "LARGE"	Collected (Source: Investigator) Annotated CRF [11]
	VSTESTCD = "HEIGHT" (Height)	Height in Orig U	float	5.1		Collected (Source: Investigator) Annotated CRF [11]
	VSTESTCD = "PULSE" (Pulse Rate)	Pulse Rate in Orig U	integer	2		Collected (Source: Investigator) Annotated CRF [11]
	VSTESTCD = "SYSBP" (Systolic Blood Pressure)	Systolic Blood Pressure in Orig U	integer	3		Collected (Source: Investigator) Annotated CRF [11]
	VSTESTCD = "WEIGHT" (Weight)	Weight in Orig U	float	5.1		Collected (Source: Investigator) Annotated CRF [11]
VSORRESU VLM		Original Units	text	20		Collected (Source: Investigator) Annotated CRF [11]
	VSTESTCD = "HEIGHT" (Height) and COUNTRY IN ("CAN", "MEX")	Height: Original Units MC	text	5	Unit (UH_MC) • "cm" = "Centimeter"	Collected (Source: Investigator) Annotated CRF [11] The data submitted only includes subjects in the USA since other sites did not enroll any subjects. Join any Subject Level dataset with the Demographics dataset based on [IG.datasetname]IT.USUBJID = [IG.DM]IT.USUBJID, assuming 'IG.datasetname' is the OID of the ItemGroupDef that defines the subject-level dataset to be joined with the Demographics dataset.
	VSTESTCD = "HEIGHT" (Height) and COUNTRY = "USA"	Height: Original Units NMC	text	5	Unit (UH_NMC) • "IN" = "Inch"	Collected (Source: Investigator) Annotated CRF [11] Join any Subject Level dataset with the Demographics dataset based on [IG.datasetname]IT.USUBJID = [IG.DM]IT.USUBJID, assuming 'IG.datasetname' is the OID of the ItemGroupDef that defines the subject-level dataset to be joined with the Demographics dataset.
	VSTESTCD = "WEIGHT" (Weight) and COUNTRY IN ("CAN", "MEX"	Weight: Original Units MC	text	4	Unit (UW_MC) • "kg" = "Kilogram"	Collected (Source: Investigator) Annotated CRF [11] The data submitted only includes subjects in the USA since other sites did not enroll any subjects. Join any Subject Level dataset with the Demographics dataset based on [IG.datasetname]IT.USUBJID = [IG.DM]IT.USUBJID, assuming 'IG.datasetname' is the OID of the ItemGroupDef that defines the joined with the Demographics dataset.

STUDYID	DOMAIN	USUBJID	VSSEQ	VSLNKID	VSLNKGRP	VSTESTCD	VSTEST	VSORRES	VSORRESU	VSSTRESC	VSSTRESN	VSSTRESU	VSLOBXFL	VISITNUM	VISIT	VSDTC	EPOCH
	VS					WEIGHT	Weight		kg			kg					

Challenge: Manage the versionning of Metadata







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Conclusion

Conclusion/Ouverture

Le M11 est en voie d'adoption par la FDA, l'Europe et le Japon?

Risque:

Allons-nous vers un processus global contrôlé par les instances réglementaires….

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Merci

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Questions??

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